



REVIEW ARTICLE

Osteoporosis: Bisphosphonate Therapy in Postmenopausal Women

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Abstract

Osteoporosis is the deterioration of bone tissue and strength, which leads to an increased risk of fractures. Postmenopausal women are at increased risk for osteoporosis. Bisphosphonates have long been the mainstay of osteoporosis treatment to prevent fractures, especially hip fractures by increasing bone mineral density. Extending treatment to up to 10 years is currently recommended. In lieu of possible adverse events such as atypical fractures and osteonecrosis of the jaw, drug holidays are an important consideration although research is currently inconclusive. Providers need to consider individual patient factors and tailor treatment to individual patient circumstances.

Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, which leads to a high possibility of fractures due to bone weakness [1]. According to the World Health Organization (WHO) diagnostic classification, osteoporosis is defined by Bone Mineral Density (BMD) at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young healthy adult reference population. The reference group is typically a healthy 20 - 29-year-old. Osteopenia, which is low bone mass, typically occurs as a precursor to osteoporosis. A patient is osteopenic when bone density is between 1 and 2.5 standard deviations below the BMD reference mean [1]. Recognizing osteopenia is an important step in the prevention of osteoporosis. Since postmenopausal women are at increased risk of osteoporosis, detection and treatment of osteoporosis are important to the overall health and wellness this population.

Knowing the current bone density screening guidelines and recommendations for treatment is essential. The focus of this review is the examination of evidence regarding the efficacy of bisphosphonates for prevention of fractures in postmenopausal women. Common and serious side effects associated with bisphosphonate use are included in this discussion.

Background

An estimated 44 million Americans are affected by osteoporosis, while another 34 million Americans are at an increased risk for osteoporosis due to low bone mass [2]. The risk of osteoporosis increases with age, certain chronic conditions, and lifestyle factors. Osteopenia and osteoporosis are often asymptomatic until an individual fall and sustains a fracture. Women are at a higher risk of developing osteoporosis. The American Congress of Obstetricians and Gynecologists (ACOG) reports that females sustain 80% of all hip fractures (2012) [3]. More than half of all fragility fractures arise in women 75 years and older [4].

Despite increased awareness of the magnitude and consequences of osteoporosis and specific recommendations for screening and treatment osteoporosis is under detected and inadequately treated in the United States [5]. Since the National Osteoporosis Foundation (NOF) first published The Clinician's Guide to Prevention and Treatment of Osteoporosis in 1999, there have been concerns that some patients are not being given appropriate education and direction about prevention of bone loss. Many patients are not receiving appropriate testing to diagnose osteoporosis or establish osteoporosis risk. Perhaps most importantly, many patients

who have osteoporosis-related fractures are not being diagnosed with osteoporosis and are not receiving any of the FDA-approved, effective therapies [1]. A clear understanding of the diagnostic recommendations along with treatment efficacy could improve the treatment of this potentially fatal disease.

Osteoporosis can affect any bone. However, the hip, spine, and wrist are most likely to be affected. Thus, a Dual X-ray Absorptiometry (DXA) scan, which is currently the gold standard for screening and diagnosing osteoporosis focuses on these areas. Fracture risk is determined by a combination of BMD and clinical risk factors. Fracture risk can also be calculated using the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX) [6]. The FRAX was developed by the WHO task force in 2008 to provide a prediction tool for assessing an individual's risk of fracture in order to provide general clinical guidance for treatment decisions. Using the FRAX, a clinician can calculate fracture risk with or without a BMD measurement of the femoral neck. The FRAX calculation estimates the risk and probability of fracture in the next 10 years in untreated patients ages 40 to 90 years of age. Factors utilized in the FRAX calculation are age, sex, height, weight, previous fracture, history of a parent with hip fracture, treatment with glucocorticoids, alcohol use, diagnosis of rheumatoid arthritis, BMD when available and lifestyle factors of smoking and alcohol use [7]. All of these risk factors are important to consider when deciding screening and treatment for individual patients.

Risk Factors

Poor nutrition such as low calcium and Vitamin D consumption and a high salt intake increases the risk for osteoporosis. Excessive thinness (BMI < 20) also places an individual at a greater risk. Lifestyle factors that increase risk for osteoporosis include alcohol abuse, inadequate physical activity, and active or passive exposure to cigarette smoking. A general decline in condition or health including frailty (e.g., unable to rise from chair unassisted), frequent falls, and immobilization are red flags for risk of osteoporosis. A personal history of fracture without substantial trauma, and hip, wrist, or spine fracture without substantial trauma in a 1st degree relative ≥ 50 are additional factors to consider [8]. Non-modifiable medical conditions that can increase the rate of bone loss include (a) Cystic fibrosis; (b) Hyperthyroidism; (c) Hypopituitarism; (d) Hypogonadism; (e) Cushing disease; (f) Hyperparathyroidism; (g) Celiac disease; (h) Multiple myeloma; (i) Renal disorders; (j) Idiopathic hypercalciuria; (k) Muscular dystrophy; (l) Paraplegia/quadriplegia [1]. Common medications that increase the risk for osteoporosis are corticosteroids, proton pump inhibitors, anti-epilepsy drugs, medroxyprogesterone acetate, selective serotonin reuptake inhibitors, thiazolidinediones, and thyroxine [9].

Lifestyle Modification to Reduce Risk

Deficiencies in protein, calcium, and Vitamin D increase risk for bone loss. All postmenopausal women should consume adequate protein, calcium and Vitamin D from diet, sunlight, or supplementation. Lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health [1]. Providers should advise consumption of 1,000 mg calcium per day for men 50-70; 1,200 mg per day for women 51 and older and men 71 and older and incorporation of dietary supplements if diet is insufficient. The average daily dietary calcium intake in adults age 50 and older is 600 to 700 mg per day, so supplementation is often necessary [1].

Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance, and decreasing risk of falling [1]. Many patients with osteoporosis will need more than the general recommendation of 800-1,000 IU of Vitamin D per day for individuals age 50 and older. The safe upper limit for vitamin D intake for the general adult population was increased to 4,000 IU per day [1]. A meta-analysis of studies in postmenopausal women found a significant reduction in hip and nonvertebral fractures with vitamin D supplementation at doses of 700 to 800 IU/day or more [9].

To promote bone health, all adults are encouraged to practice healthy lifestyle habits. Providers should prescribe at least 30 minutes of exercise per day with the addition of weight bearing or muscle strengthening exercises to reduce fall and/or fracture risk. Patients should avoid alcohol use in excess of 2 drinks per day, limit caffeine intake, and cease smoking to reduce risk of bone loss.

Since the majority of osteoporosis-related fractures result from falls, providers should evaluate fall risks. Strategies to prevent falls include (a) Assistive devices in bathrooms; (b) Eliminating obstacles in the walking path; (c) Removing loose throw rugs; (d) Avoiding slippery conditions; and (e) Eliminating low level lighting increase risk of falling but can be modified. Correcting sensory deficits can also reduce risk of falls [1].

The American Association of Clinical Endocrinologists (AACE) also recommends nonpharmacologic interventions such as the use of proper body mechanics, use of hip protectors and other protective measures to reduce the risk of falling [9]. Physical therapy and occupational therapy can teach strengthening exercises and improved body mechanics. Therapists may also assess the home setting and identify risks for falling that might be modified and safety concerns that could be addressed with the addition of assistive devices or tools.

Impact of Fracture

Fractures tend to be grouped as vertebral and non-vertebral fractures. The majority of non-vertebral

fractures are hip and wrist fractures. Hip fractures are the most serious complication of osteoporosis. One reason it is so important to reduce the risk of fracture is because of the increased morbidity, particularly with hip fractures. Mortality increases by 30% during the first year after a person sustains a hip fracture and the risk of hip fracture in the opposite hip increases by more than two-fold after a previous hip fracture [10]. The patient who suffers a hip fracture also experiences a decrease in mobility, quality of life and increased financial burden due to cost of care [11]. Of patients who were able to walk independently prior to fracture, only half are able to do so one year after. More than half of patients who survive hip fractures will require skilled care in a facility setting, and many will have permanent disability [9].

Current Guidelines

Screening

The National Osteoporosis Foundation [1,3,9] and the United States Preventative Services Task Force [12] recommend BMD testing every two years for women age 65 and older regardless of clinical risk factors. Each of these organizations also recommend BMD testing for women ages 50-69, based on their risk factor profiles. Adults who are younger than 65 with certain conditions such as rheumatoid arthritis or those who are taking certain medications such as long-term glucocorticoids (more than three months) should be considered for BMD testing. Those who have had an adult age fracture associated with low bone mass or bone loss should be considered for BMD testing even if they are younger than 65.

Authors of the ACOG guidelines for screening and treatment of osteoporosis, suggest screening for secondary causes of osteoporosis in specific situations. These include the presence of fractures in a relatively young postmenopausal woman or for a woman with a Bone Mineral Density (BMD) lower than would be expected for her age. A complete blood count, metabolic profile, a 24-hour urinary calcium level, thyroid-stimulating hormone, and 25-hydroxyvitamin D are all recommended first tier testing. Some patients may benefit from a referral to a clinical endocrinologist as the next step.

The NOF [1] is more specific related to screening and treatment. The organization also recommends BMD testing for postmenopausal women and men over age 50 who have had a fracture during adulthood. The testing is done in order to diagnose osteoporosis and determine severity. Annual height checks are also included in NOF screening guidelines.

The NOF [1] and AACE [9] recommend BMD testing one to two years after initiating medical therapy for osteoporosis. The NOF [1] recommend DXA every two years thereafter to monitor treatment efficacy. However, authors of the AACE guidelines [9] suggest follow-up

scans could be less frequent once the findings are stable. Authors of the ACOG guidelines [3] report that DXA scans are not recommended more often than every 2 years. In addition, if no new risk factors are identified, DXA monitoring of therapy should not be repeated once BMD has been determined to be stable or improved. The USPSTF [12] and NOF [1] specify testing be completed in facilities that use quality assurance measures. Also, follow-up DXA scans should be in the same facility, with the same machine, and if possible, with the same technologist [9].

Treatment with bisphosphonates

In addition to the nonpharmacologic recommendations, bisphosphonates are a first-line therapy worldwide and a mainstay of primary prevention of fracture. Bisphosphonates are frequently prescribed for osteoporosis, with more than 14 million prescriptions dispensed yearly in the United States. Patients treated with these drugs experience increases in bone mineral density and a reduction in vertebral and nonvertebral fractures for osteoporosis. They are also used as secondary prevention in patients with previous fracture.

The NOF [1] recommends pharmacologic treatment for patients with non-vertebral or vertebral (clinical or asymptomatic) fractures. Therapy should also be initiated for those with T-scores below -2.5 at the femoral neck, total hip or lumbar spine by DXA, as this is consistent with a diagnosis of osteoporosis. Pharmacologic treatment is also recommended for postmenopausal women and men age 50 and older who meet the criteria for osteopenia as evidence by BMD T-score between -1.0 and -2.5 at the femoral neck, total hip or lumbar spine by DXA. A patient with a 10-year hip fracture probability > 3 percent (based on the WHO FRAX) or a 10-year major osteoporosis-related fracture probability > 20 percent (based on the WHO FRAX) should also have pharmacologic treatment NOF [1].

Bisphosphonates are the most prescribed drugs for treatment of osteoporosis [9]. The Food and Drug Administration (FDA) approved bisphosphonates for treatment of osteoporosis are alendronate, alendronate plus D, ibandronate, risedronate and zoledronic acid. The NOF [1] does not recommend one drug over another. The choice is patient specific, but alendronate tends to be a first line treatment because of its broad spectrum of antifracture efficacy and low cost. The AACE [9] recommends bisphosphonates: Alendronate, risedronate, and zoledronic acid as first line therapy and offer guidance on the monitoring and duration of treatment.

Calcium and Vitamin D

Current guidelines recommend education and treatment with calcium and Vitamin D in all patients to prevent bone loss and slow bone loss if osteopenic or osteoporotic [1,9]. Consumption of adequate daily calcium and vitamin D is a safe and inexpensive way to help re-

duce fracture risk. Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of osteoporotic fracture [13].

Methods

In order to facilitate updates to this review in the future, the search strategy is presented. The electronic search was performed using Ebsco Host to search CINAHL and MEDLINE. The English language search terms used were osteoporosis, elderly female, diphosphonates, hip fracture, and efficacy. The language was restricted to English. The date limiters were from 2010 to 2015. The search was limited to full text articles, academic journals, species (human), sex (female), and aged greater than 65 years.

A total of 321 articles, that evaluated bisphosphonate efficacy for elderly osteoporotic women, were identified in the literature search. Only 30 potential articles met initial inclusion criteria and were selected for review. This literature focuses on studies of bisphosphonate efficacy to prevent hip fractures but did not exclude studies that included other nonvertebral or vertebral fractures. Studies were included whether bisphosphonate therapy was initiated before or after initial fracture. Studies that did not exclude secondary causes for osteoporosis and men were excluded.

Bisphosphonates for fracture prevention

There is a large body of evidence supporting the use and efficacy of oral bisphosphonates in hip fracture prevention. Multiple research studies and current practice guidelines support the use of oral bisphosphonates to prevent both vertebral and non-vertebral fractures in osteoporotic women. Evidence in support of bisphosphonates in other nonvertebral and vertebral fracture prevention has recently increased.

The efficacy of oral ibandronate on vertebral fractures was demonstrated by researchers of a randomized, double-blind study BONE, conducted in North America and Europe. Oral ibandronate in doses of either 2.5 mg daily or 20 mg every other day for 12 doses every 3 months led to a significant reduction in vertebral fracture risk [14]. Years later, [15] performed a Randomized Control Trial (RCT) in Japan and confirmed in the Asian population what the Vertebral Efficacy with Risedronate Therapy in North America, VERT-NA, had shown for whites. In the VERT-NA trial, oral risedronate demonstrated a significant reduction in vertebral fracture risk. Nakamura, et al. demonstrated the vertebral fracture risk reduction in the Asian population with both oral and intravenous bisphosphonate therapy.

Many RCTs investigations have independently concluded that intravenous bisphosphonates are effective in limiting the incidence of vertebral fractures. A randomized, double blind trial with once yearly intrave-

nous zoledronic acid at 5 mg doses was performed by [4]. They demonstrated an association between the annual dosing of zoledronic acid and significant reduction in risk of new fractures, both vertebral and nonvertebral. In an RCT performed in China researchers similarly concluded that two years of treatment with intravenous Zoledronic acid reduces fracture risk for osteoporotic women [16].

Intravenous bisphosphonate therapy has also been found to be effective in preventing hip and other non-vertebral fractures. [16] demonstrated the efficacy of two years of treatment with intravenous zoledronic acid for nonvertebral fracture prevention. In [4] concluded that intravenous or zoledronic acid is effective in reducing nonvertebral clinical fracture in a meta-analysis [17] reported that both alendronate and zoledronate are effective in increasing BMD to prevent nonvertebral and vertebral fractures.

Duration of therapy

Many researchers based on study findings support long-term bisphosphonate treatment, which is defined as treatment of greater than 5 years. [18] and [19] both found that use of bisphosphonates long-term, up to 7 years and 10 years respectively show continued increases in BMD without adverse skeletal events. Other researchers have found benefits in continuing bisphosphonate treatment for up to 10 years [20,21]. In the FLEX trial women who discontinued therapy at 5 years, which is the current standard of care, experienced a 5.3% prevalence of vertebral fractures at 10 years as opposed 2.4% of those who continued treatment for 10 years. Interestingly, there was no difference in prevalence of nonvertebral fractures between the 5- and 10-year treatment groups [21]. However as recently as [22] argued in that there remains insufficient evidence to support benefits of treatment beyond 3-5 years. Thus, providers must use their own clinical judgment based on individual patient situations.

Consideration of residual effects may aid in determining the timing of bisphosphonate medication discontinuation. The residual benefits of bisphosphonate therapy appear to last for 2-5 years after discontinuation whether treatment ends at 5 years or later. Of note, this benefit is only seen in those with good medication adherence during the treatment years, for at least 2 consecutive years and for those whose T-score was -1.0 to -2.5 (osteopenic) or > -1.0 (normal) at discontinuation.

The risk of atypical fractures and osteonecrosis of the jaw increase with increase as the duration of bisphosphonate therapy increases. A "drug holiday" may be considered for patients with mild osteoporosis who have had 4-5 years of stability. Stability is categorized as increasing or stable BMD and no fractures and a T score better than -2.5 . A "drug holiday" of 1 to 2 years may be considered after 10 years of treatment for patients if

fracture risk is high. A patient with advanced age, frailty, prior fractures, glucocorticoids, and very low T-scores are considered high fracture risk. Bone mineral density and bone turnover markers should be monitored during a drug holiday period. Therapy should be reinstated if bone density declines substantially, bone turnover markers increase, or a fracture occurs [9].

Oral versus intravenous therapy

Based on current research the intravenous and oral routes are equally efficacious. Determination of which route is best for a given patient should be based on individual patient factors, such as tolerance and adherence. A few researchers have compared the two routes for safety and efficacy.

Most recently, [17] performed a meta-analysis of 17 studies comparing the safety and efficacy of oral alendronate and intravenous zoledronate. Comparisons were done by specific fracture risk, for hip, vertebrae, and wrist. A significant relative risk reduction was observed for both alendronate and zoledronate of 39% and 38%, respectively. While the overall fracture risk reduction is nearly equal, [17] found that for prevention of vertebral fractures intravenous therapy, zoledronate, may be more effective in preventing vertebral fractures.

The efficacy and safety of oral daily risedronate versus intravenous ibandronate were also investigated in a randomized double-blind study by [15]. Researchers concluded that intravenous ibandronate was equally efficacious to oral therapy, risedronate for new or worsening vertebral fracture over 3 years. Of note the findings were dose dependent. The 1 mg/month dose of ibandronate was more effective in reducing fracture risk than the lower dose of 0.5 mg/month.

Cost effectiveness

The aging population worldwide has caused an increasing economic burden upon society, related to health issues, osteoporosis being one facet. Hip fractures result in increased morbidity resulting in increased cost to the health care system as well as the individual. Thus ensuring health care spending is prudent related to osteoporosis treatments and fracture prevention is significant. A strategy for cost-saving has been to consider withholding treatments that may not be cost effective for certain groups, commonly those with shorter life expectancies.

Pham, Datta, Weber, Walter & Colon-Emeric [23] performed a cost versus benefits analysis that dispelled bisphosphonate treatment expense myths. The investigators found an increased cost effectiveness for older ages, even the extremes of old age, up to age 90 for initiating treatment, when treating osteoporosis in women for 5 years with oral bisphosphonates. When considering cost treatment with bisphosphonates against cost of an acute hip fracture in the first year

and possible long term care costs, researchers found that treatment with an oral bisphosphonate for 5 years was cost effective for all women without a history of hip fracture, irrespective of quartile of life expectancy. Consequently, advanced age should not prevent consideration of osteoporosis treatment based on cost effectiveness.

While withholding treatments in those with shorter life expectancies is the current recommendation, specific criteria as to qualifying as a shorter life expectancy has not been determined. A secondary analysis of the HORIZON recurrent fracture trial is worth noting. In this analysis by [24] treatment with zoledronic acid in cognitively impaired patients with a life expectancy of just six months or more was found to be worthwhile. While this was just one study, the growing population of cognitively impaired elderly is growing, making confirmation of this data valuable for the future treatment of this population [24]. Researchers have studied the question of cost versus benefits of bisphosphonate therapy in terms of medication costs. [25] determined that for every 228 individuals treated with oral daily bisphosphonates one hip fracture would be prevented. They calculated the associated cost in preventing one fracture to be £76,352 or \$110,733.31.

Serious Adverse Effects

Atypical fracture

Concerns have arisen about atypical subtrochanteric femur fractures related to long-term bisphosphonate use, typically greater than 5 years [26]. It has been hypothesized that this prolonged and severe suppression of bone turnover may have negative effects by causing accumulation of microdamage and localized highly mineralized bone. This may potentially increase the risk of stress fractures with normal activities and no known trauma [19]. Several reviews of atypical fracture found the average median length of treatment to be around five years with a range from 1-10 years and increased risk with glucocorticoid use [19,27].

Due to the concern of atypical fracture, a task force was appointed by the American Society of Bone and Mineral Research to review this important concern. The group concluded that long-term bisphosphonate use does increase the relative risk of atypical fractures; however, the absolute risk is low. The risk for atypical fracture may rise with duration of bisphosphonate exposure of greater than three years. When an atypical fracture has been diagnosed, the bisphosphonate should be stopped to decrease the risk of atypical fracture in the opposite leg [28].

Patients with atypical fractures commonly present with unilateral or bilateral dull or aching pain in the groin or thigh. The time from the onset of pain to the time of diagnosis is usually 1-2 weeks [29]. For a patient taking a bisphosphonate greater than 5 years or who

is taking a concomitant glucocorticoid or PPI, an x-ray should be ordered. When a Proton Pump Inhibitor (PPI) is prescribed in conjunction with a bisphosphonate in the elderly population, the patient could be at increased risk for atypical fracture. Proton pump inhibitors interfere with the absorption of calcium and bisphosphonates thus affecting their anti-fracture efficacy and have been incriminated in osteoporotic fractures [30]. As referenced above, glucocorticoids used concomitantly also place a patient at increased risk due to suppression of bone turnover” [26].

Osteonecrosis of the jaw

Case reports and case series have associated Osteonecrosis of the Jaw (ONJ) with patients taking bisphosphonates compared to those who have not been on bisphosphonates. Bisphosphonates have a long half-life following cessation and may be associated with delayed healing and even the devastating complication of ONJ. Treatment with bisphosphonates may exert an inhibitory effect on oral epithelial growth. These drugs suppress bone turnover which may contribute to ONJ in patients who have mucosal damage following dental extraction, irritation from ill-fitting dentures or insertion of dental implants complicated by infection and bone necrosis [31].

Prior to initiating bisphosphonate therapy, a dental review should be completed so any invasive dental procedures can be performed before the bisphosphonate is started. Patients should be instructed to promptly report any new dental symptoms, especially dental pain, swelling or exposed bone [31]. The risk of developing ONJ with oral bisphosphonate use is low but is substantially greater for patients receiving IV bisphosphonate therapy, particularly for metastatic cancer to the bone. Most, 95%, of the cases of osteonecrosis of the jaw have occurred in patients who have cancer and were receiving higher doses of IV Zoledronic acid [2].

Additional adverse effects

The adverse effects vary by drug and patient physiology with the most common adverse effects being gastrointestinal; specifically reflux, esophagitis, and esophageal ulcers. The gastrointestinal toxicity of oral bisphosphonates is likely to be a local, rather than systemic effect and is often related to taking the medication incorrectly. “Trials have reported esophageal ulcerations from all bisphosphonates except intravenous Zoledronic Acid (ZA)” [2]. If a patient reports gastrointestinal intolerance to alendronate, risedronate may have fewer side effects. In clinical trials, the incidence of gastrointestinal side effects associated with risedronate was not different from placebo [6]. Intravenous pamidronate may be a good alternative for oral bisphosphonates for patients with gastrointestinal intolerance during treatment with oral bisphosphonates [32].

Intravenous Zoledronic Acid (ZA) 5 mg is associated with an increased incidence of pyrexia, myalgia, and influenza-like illness within three days of infusion when compared to placebo [4]. Adverse reactions following transfusion of zoledronic acid may be contributed to a rapid release of pro-inflammatory cytokines from circulating T cells which occurs most commonly after the initial dose. Also, prior to each ZA infusion, clinicians should measure serum creatinine and ensure adequate hydration to prevent renal impairment or acute renal injury [6].

Adverse effects from bisphosphonates are not unusual, but rarely cause the need to discontinue the medication. In the meta-analysis performed by Serrano, Begoña, Anitua, Cobos, & Orive [17], there was very little difference in the percentage of patients who discontinued alendronate (7.86%) versus placebo (7.58%). The percentage of discontinuation with zoledronic acid was 2.05% versus 1.79% with placebo.

Contraindications

Due to a risk of kidney injury, bisphosphonates are generally not recommended for those with a creatinine clearance below 30-35 ml/min or in patients with acute renal impairment [6]. Due to the increased risk of gastrointestinal side effects, oral bisphosphonates should not be used at all in patients with significant esophageal disorders [6]. Bisphosphonates are also contraindicated in any patients who is not able to stay upright for at least 30 to 60 minutes [6].

Treatment adherence

Adherence and persistence to osteoporosis therapies are poor as is the case for other “silent” conditions such as hypertension and hyperlipidemia [9]. Roughly 50-75% of women, prescribed medication for osteoporosis or osteopenia, are no longer taking bisphosphonates one year after beginning treatment [33]. Bisphosphonates need to be taken in a specific manner and for at least a year for evidence of improvement of Bone Mineral Density (BMD) and protection against fracture. Poor adherence leads to lower therapeutic efficacy, weaker suppression of bone resorption, smaller increases in BMD, less reduction in fracture risk, and drug wastage [33].

Many patients do not follow specific directions for taking the oral bisphosphonates. Orally administered bisphosphonates must be taken after a prolonged fast, usually the first thing in the morning, and washed down with a full glass of water in order to minimize the chance that the tablet will stick in the esophagus. Nothing other than water should be taken for 30 minutes to 60 minutes depending on specific bisphosphonate being taken [9]. Special efforts should be made to explain to the patient the need for osteoporosis and osteopenia therapy and what to expect when taking the medication. In addition it is important to schedule periodic follow-up to

ensure that the medication is still being used correctly and appropriately.

Conclusion

Bisphosphonate therapy is known to improve BMD to aid in prevention of future fractures in persons with osteoporosis. Bisphosphonates demonstrate reduction of the incidence of vertebral, hip and other nonvertebral fractures. According to current research both oral and intravenous preparations are equally efficacious in fracture prevention. Current research indicates that the benefits of bisphosphonate therapy outweigh the risks for most patients. Furthermore, researchers have demonstrated the cost-efficacy of bisphosphonate therapy for patients even the advanced elder, aged greater than 75.

In regard to the controversy regarding appropriate length of treatment, current evidence supports safe use of oral risedronate for up to seven years consecutively and oral alendronate for up to 10 years. Patients do not become refractory to treatment within these durations of therapy and therefore patients with the highest risks for fractures related to osteoporosis or a T-score of < -2.5 after treatment should continue therapy for 10 years. Unfortunately increases in occurrence of fragility fractures or atypical fractures are demonstrated with long-term use. Even with recent increased attention, occurrences of atypical fractures remain rare. However, providers should keep possible adverse events such as atypical fractures and osteonecrosis of the jaw in mind.

A drug holiday of 2-5 years may be indicated as residual benefits appear to last for this extent of time. Patients should be monitored with DEXA scans every 2 years for declining BMD, which may indicate the need to resume bisphosphonate therapy. New fractures should also suggest to the provider a need to resume bisphosphonate therapy.

Treatments should be tailored to the individual patient's clinical picture, needs, any side effects and cost constraints. Providers must keep in mind that adherence is essential for full benefits of bisphosphonate therapy and choose treatments that are most likely to yield best adherence. It is key for providers to consider individual patient factors and tailor treatment to individual patient needs.

References

- National Osteoporosis Foundation (NOF) (2014) Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis Int* 25: 2359-2381.
- Qaseem A, Snow V, Shekelle P, Hopkins R, Forciea MA, et al. (2008) Pharmacologic Treatment of Low Bone Density or Osteoporosis to Prevent Fractures: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med* 149: 404-415.
- The American Congress of Obstetricians and Gynecologists (2012) Practice Bulletin 129: Osteoporosis. *Obstetrics & Gynecology* 120: 718-734.
- Boonen S, Black D, Colón-Emeric C, Eastell R, Magaziner J, et al. (2010) Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. *J Am Geriatr Soc* 58: 292-299.
- Nelson HD, Haney EM, Chou R, Dana T, Fu R, et al. (2010) Screening for Osteoporosis: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 77. AHRQ Publication No. 10-05145-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality.
- Harold R (2015a) The Use of Bisphosphonates in Postmenopausal Women with Osteoporosis. In J. Mulder. (Ed.). UpToDate.
- Fracture Risk Assessment Tool (2016) American College of Rheumatology.
- University of Michigan Health System (2011) Osteoporosis: prevention and treatment. Ann Arbor (MI): University of Michigan Health System.
- Watts NB, Bilezikian JP, Camacho PM, Greenspan SL, Harris ST, et al. (2010) AACE American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract* 3: 1-37.
- Kandel L, Schler D, Brezis M, Liebergall M, Mattan Y, et al. (2013) A simple intervention for improving the implementation rate of a recommended osteoporosis treatment after hip fracture. *Endocrine Practice* 19: 46-50.
- Beaupre LA, Morrish DW, Hanley DA, Maksymowych WP, Bell NR, et al. (2011) Oral bisphosphonates are associated with reduced mortality after hip fracture. *Osteoporosis Int* 22: 983-991.
- U.S. Preventive Services Task Force (2011) Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 154: 356-364.
- Larsen ER, Mosekilde L, Foldspang A (2004) Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 19: 370-378.
- Chestnut CH III, Skag A, Christiansen C, Recker R, Stakkestad JA, et al. (2004) Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19: 1242-1249.
- Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, et al. (2013) Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. *Calcif Tissue Int* 93: 137-146.
- Bai H, Jing D, Guo A, Yin S (2013) Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. *J Int Med Res* 41: 697-704.
- Serrano AJ, Begoña L, Anitua E, Cobos R, Orive G (2013) Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. *Gynecol Endocrinol* 29: 1005-1014.
- Mellstrom DD, Sorenson OH, Geomaere S, Roux C, Johnson TD, et al. (2004) Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int* 75: 462-468.

19. Trotter CC, Pfister AK, Whited BA, Goldberg TH, Artz SA (2011) A controversy: linking atypical femoral fractures to bisphosphonate therapy. *W V Med* 107: 8-13.
20. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, et al. (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 350: 1189-1199.
21. Schmidt GA, Horner KE, McDanel DL, Ross MB, Moores KG (2010) Risks and benefits of long-term bisphosphonate therapy. *Am J Health Syst Pharm* 67: 994-1001.
22. Rosenthal Y, Arami A, Kosashvili Y, Cohen N, Sidon E, et al. (2014) Atypical fractures of the femur related to prolonged treatment with bisphosphonates for osteoporosis. *Isr Med Assoc J* 16: 78-82.
23. Pham AN, Datta SK, Weber TJ, Walter LC, Colón-Emeric CS (2011) Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. *J Am Geriatr Soc* 59: 1642-1649.
24. Prieto-Alhambra D, Judge A, Arden NK, Cooper C, Lyles KW, et al. (2014) Fracture prevention in patients with cognitive impairment presenting with a hip fracture: secondary analysis of data from the HORIZON Recurrent Fracture Trial. *Osteoporos Int* 25: 77-83.
25. Arias LH, Treceño C, García-Ortega P, Rodríguez-Paredes J, Escudero A, et al. (2013) Hip fracture rates and bisphosphonate consumption in Spain. An ecologic study. *Eur J Clin Pharmacol* 69: 559-564.
26. Rizzoli R, Akesson K, Bouxsein M, Kanis JA, Napoli N, et al. (2011) Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporos Int* 22: 373-390.
27. Powell D, Bowler C, Roberts T, Garton M, Matthews C, et al. (2012) Incidence of serious side effects with intravenous bisphosphonate: a clinical audit. *QJM* 105: 965-971.
28. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, et al. (2014) Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 29: 1-23.
29. Gopal GK, Tam KL, Krishnan SP, Maddern IL (2014) Bisphosphonate-associated atypical subtrochanteric femur fractures in the older patient. *The New Zealand Medical Journal* 127: 81-85.
30. Abrahamsen B, Eiken P, Eastell R (2011) Proton pump inhibitor use and the antifracture efficacy of alendronate. *Arch Intern Med* 171: 998-1004.
31. Wong PK, Borromeo GL, Wark JD (2013) Bisphosphonate-related osteonecrosis of the jaw in non-malignant bone disease. *Rheumatol Int* 33: 2189-2198.
32. Eekman DA, Vis M, Bultink IE, Derikx HJ, Dijkmans BA, et al. (2009) Treatment with intravenous pamidronate is a good alternative in case of gastrointestinal side effects or contraindications for oral bisphosphonates. *BMC Musculoskelet Disord* 10: 86.
33. Lai PS, Chua SS, Chew YY, Chan SP (2011) Effects of pharmaceutical care on adherence and persistence to bisphosphonates in postmenopausal osteoporotic women. *J Clin Pharm Ther* 36: 557-567.